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Pulmonary hypertension associated with ponatinib therapy

To the Editor:

Over 50 drugs, including anorexigens, abused substances and recently the tyrosine kinase inhibitor (TKI) dasatinib, have been temporally and/or mechanistically related to the development of pulmonary arterial hypertension (PAH) in humans (where the evidence base for causality is wide ranging) and in animal models [1–3]. The TKIs imatinib, dasatinib, nilotinib and bosutinib are available to treat chronic myelogenous leukaemia (CML) and acute lymphoblastic leukaemia. These drugs are associated with distinctive respiratory adverse effects (AEs), including pleural and/or pericardial effusion, PAH (an AE so far almost exclusively restricted to dasatinib) and pulmonary infiltrates [1, 4–6]. The novel TKI ponatinib is prescribed for the same indications as above, in patients whose haematological malignancy has become resistant to, or who develop intolerance to the earlier TKIs [7]. Here, we present a female CML patient with prior exposure to dasatinib who developed PAH 6 months into ponatinib therapy, an association that has not previously been reported. Signs and symptoms of PAH improved following drug discontinuation and institution of targeted anti-PAH therapy.

The patient was a Caucasian woman who was diagnosed with CML in 2006, then aged 62 years. Her history included moderate systemic hypertension, dyslipidaemia and obesity (body mass index 38 $kg \cdot m^{-2}$). She was on long-term treatment with atorvastatin, celiprolol, furosemide, allopurinol, amitriptyline and alprazolam. Treatment for her CML included hydroxycarbamide (500 mg twice daily in July–August, 2006), imatinib (600 mg once daily between July 2006 and October 2008) and nilotinib (400 mg twice daily between October 2008 and January 2011). Dasatinib (100 mg once daily) was started in January 2011. In January 2013, a right-sided lymphocyte-rich (92%) pleural exudate developed (with proteins 48 $g \cdot L^{-1}$). Dasatinib was considered causative and was withdrawn. 1 month afterwards, the effusion was less on imaging and dasatinib was resumed at 100 mg once daily. The effusion relapsed within 6 weeks. Dasatinib was changed to ponatinib (45 mg once daily) in April 2013. Transthoracic echocardiography in May 2013 was normal. N-terminal pro-brain natriuretic peptide (NT-proBNP) was 133 $pg \cdot mL^{-1}$ (normal is <167 $pg \cdot mL^{-1}$).

In October 2013, dyspnoea developed, progressing to New York Heart Association (NYHA) class IV. The NT-proBNP was 1500 $pg \cdot mL^{-1}$. Following a warning from the US Food and Drug Administration on ponatinib-associated arterial and venous thromboses [8], ponatinib was set at 30 mg once daily. Aspirin (100 mg daily) was started. The work-up for dyspnoea included a Doppler ultrasound, which showed right leg vein thrombosis, and fluindione was started. A new echocardiogram disclosed right ventricular dilatation and paradoxical septal motion. Systolic pulmonary artery pressure (PAP) was estimated at 100 mmHg. A right-sided catheterisation confirmed severe precapillary pulmonary hypertension with a mean PAP of 52 mmHg, normal pulmonary wedge pressure of 12 mmHg, low cardiac index (1.8 $L \cdot min^{-1} \cdot m^{-2}$) and elevated pulmonary vascular resistance (12.7 Wood units). There was no acute vasodilator PAP response following inhalation of nitric oxide. An extensive PAH work-up including chest computed tomography (CT) failed to disclose an aetiology for PAH. A ventilation/perfusion scan showed perfectly homogeneous perfusion and ventilation in both lungs. Since no PAH case was known in association with ponatinib at the time, the drug was continued.

In January 2014, the patient was admitted for severe right ventricular failure. Subcutaneous treprostinil at the recommended stepwise incremental dosage, oral ambrisentan (5 mg once daily) and furosemide were given. 12 days later, she suffered a right frontal gyrus stroke, despite being on anticoagulants and antiplatelets. No haemorrhage was found on brain CT. Because of reserved neurological outcome, treprostinil was withheld and oral sildenafil (20 mg three times daily) was given in combination with ambrisentan. The possibility that ponatinib was involved in her PAH was raised. The drug was stopped, also because of venous thrombosis and stroke. At day 30, neurological signs and symptoms improved notably. In November 2014, clinical status (dyspnoea: NYHA class I), haemodynamics (table 1) and neurological status had all improved. The patient being in complete cytogenetic response, no further CML-specific drug was given (at time of writing). She remains on sildenafil and ambrisentan. The Naranjo score was 6 [9], consistent with drug (ponatinib)-related PAH.

TABLE 1 Time course of clinical symptoms and haemodynamics

	November 2013		April 2014	November 2014
	Baseline	Post nitric oxide		
Ponatinib timeline	7 months of therapy	7 months of therapy	3 months after withdrawal	10 months after withdrawal
NYHA dyspnoea functional class	IV	IV	II	I
PAP mmHg				
Systolic	83	84	59	48
Diastolic	30	29	20	18
Mean	52	51	36	30
Resting PAWP mmHg	12	12	9	12
RVP mmHg				
Systolic	86		59	49
Protodiastolic	6		3	2
Telediastolic	19		10	10
Mean RAP mmHg	15		9	10
Cardiac output L·min^{-1}	3.16	2.76	5.36	5.87
Cardiac index L·min^{-1}·m^{-2}	1.8	1.6	2.8	3.1
PVR Wood units	12.7	14.1	5.6	3.1

NYHA: New York Heart Association; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; RVP: right ventricular pressure; RAP: right atrial pressure; PVR: pulmonary vascular resistance.

The AEs from TKIs differ according to their specific molecular target [5, 6]. Pleural effusion is a classic if not common AE from TKIs [1], whereas PAH has been almost exclusively reported with dasatinib [1, 4, 5]. We thought dasatinib was causal in the pleural effusion in our patient, because this complication is commonly observed with the drug [1, 10], and dasatinib dechallenge/readministration led to improvement and relapse, respectively. The respective roles of dasatinib and ponatinib have to be discussed as regards the vascular complications including PAH in our patient. To date, dasatinib has been associated with the development of PAH in 49 cases overall [1, 4, 11], including 27 previously published and 22 unpublished cases [3]. In all 27 published cases, dasatinib was discontinued. PAH-targeted therapy was given to 14 cases [4]. Among the 22 unpublished cases [3], dasatinib was stopped in 19 and PAH-targeted therapy was given to eight [3]. Partial or complete improvement was seen in 38 (77.6%) out of the 49 cases.

Ponatinib specifically targets the T315I resistance mutation of the BCR-ABL protein that develops in ∼15% of CML patients exposed to earlier TKIs [7]. Common ponatinib AEs include a cutaneous rash, xerostomia, abdominal pain and cytopenia [7]. The development of venous and arterial thromboses during treatment with ponatinib led to temporary withdrawal of the drug from US markets in 2013, followed by its restricted use in patients harbouring the T315I mutation [6]. Although a World Health Organization AE database on ponatinib lists eight PAH cases, including our own (access restricted to pharmacovigilance personnel), no details are given. We found no index PAH case with the use of ponatinib in the literature [1].

In performing a causality assessment, we note that there was no evidence for pulmonary hypertension on echocardiography prior to initiation of therapy with ponatinib in our patient. No other cause for her PAH was found. PAH improved following ponatinib withdrawal, although concomitant therapy with PAH-targeted therapy may have played a role. Finally, a Naranjo score of 6 was consistent with ponatinib-induced or -triggered PAH. However, one may question the role of prior exposure to dasatinib, an established aetiology for PAH [4]. In our case, dasatinib had been withheld 6 months prior to the diagnosis of PAH, and no late PAH case has been reported after dasatinib cessation [3, 4].

Tyrosine kinases may be involved in the pathophysiology of PAH [2]. Platelet-derived growth factor, autocrine fibroblast growth factor, c-kit and epidermal growth factor receptors are all potential targets for innovative anti-PAH TKI therapy [12, 13]. Conversely, the Src tyrosine kinase pathway is an essential cofactor for activation of TASK-1 (Twik-related acid-sensitive K^+ channel, subtype 1) and voltage-dependent K^+ channels (including $K_V1.5$ and calcium-activated channels), thereby maintaining low resting pulmonary artery smooth muscle cell (PASMC) tone. Inhibition of Src tyrosine kinase inactivates these channels, leading to PASMC membrane depolarisation, pulmonary vasoconstriction and late vascular remodelling [13–15]. As both dasatinib and ponatinib inhibit Src tyrosine kinase [10], it is conceivable that the Src tyrosine kinase pathway may be implicated in dasatinib-induced PAH [14]. Common targets between dasatinib and ponatinib as regards Src-mediated and other mechanisms for PAH induction are being actively explored. In the meantime, clinicians ought to stay vigilant for the possible emergence of new ponatinib-associated PAH cases.

In conclusion, we report the first ponatinib-associated PAH case. Our patient improved with cessation of exposure and PAH-targeted therapy. The reason why PAH cases are restricted to dasatinib and ponatinib, two potent Src inhibitors, and the mechanistic role of Src in this process, remain to be investigated. Leukaemia patients on TKIs need be monitored as regards the possible development of this complication.

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A case of pulmonary hypertension associated with ponatinib therapy in a chronic myelogenous leukaemia patient http://ow.ly/V8reI

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